REMARKS

In an Office Action mailed December 13, 2000, the Examiner rejected Claims 1-13. Claims 14-27 were withdrawn from consideration as being unelected by the applicants. The Examiner made final the requirement for restriction. The Examiner also required a new sequence listing and CRF, pointing out a sequence on page 9, line 3, and a pair of sequences in Figure 1C not mentioned in the Sequence Listing as filed. The Examiner also indicated that the IDS was considered with the exception of a single document said to include a list of abstracts. Claims 6-10 were rejected under 35 U.S.C. §112, first paragraph for an alleged lack of written description in the specification. Claims 1-13 were also rejected under 35 U.S.C. §112, first paragraph for an alleged lack of enablement. Finally, Claims 1-13 were rejected under 35 U.S.C. §112, second paragraph for a variety of formal matters.

No fee is believed due in connection with this response, however, should any fee be due in this or any subsequent response, please charge the fee to Deposit Account Number 17-0055. A petition for one month extension of time accompanies this response so that the response will be deemed to have been timely filed. No additional extension of time is believed due in connection with this response, but if any additional extension is required in this or any subsequent response, please consider this to be a request for the appropriate extension of time and a request to charge any extension fee to the same deposit account.

Each issue raised by the Examiner is considered separately below. In view of the amendments noted above and the arguments presented herein, the applicants respectfully request reconsideration of the merits of this patent application.

Requirement for Restriction

The Examiner made final the requirement for restriction. Claims 14-27 are canceled above without prejudice to the filing of a divisional patent application.

Sequence Listing

The Examiner identified a consensus amino acid sequence for TSPt1-like repeats on page 9, line 3 of the application. The consensus sequence is W-X_{4-5}-W-X_2-CS-X_2-CG-X_{4-5}-X-G-X_3-R-X_3-C-X_{4-27}-C-X_{8-12}-C-X_{3-4}-C. In addition to the gon-1 amino acid sequence (SEQ ID NO:2), Fig. 1C also depicts the amino acid sequences of the known murine ADAMTS-1 and the bovine P1NP proteins.

The above-noted consensus sequence as well as the ADAMTS-1 and P1NP amino acid sequences are included in the enclosed substitute sequence listing.

Information Disclosure Statement

The applicants note that a list of abstracts from a 1996 meeting containing no substantive information was not considered by the Examiner. The applicants did not intend

to bring any particular abstract to the Examiner's attention. The applicants regret the oversight.

Rejections Under 35 U.S.C. §112, first paragraph

In rejecting Claims 6-10 for lack of written description, the Examiner raised concerns over the nature of the protein recited in the claims, pointing to the scope of the target organism and the protein deemed the "target protein" by the Examiner.

Claim 6 is clarified to more clearly point out the intent of the applicants. Specifically, the amendments to Claims 1 and 6 recite certain nematodes in which the assay can function (without prejudice to the subsequent filing of a broader claim encompassing other organisms) and clarify that the protein intended is "for directing migration of the gonadal cell wherein the protein comprises a metalloprotease domain and a thrombospondin domain. In the assay disclosed by the applicants, one can readily determine whether a protein directs migration of a gonadal cell using the assay disclosed by the applicants. Amended Claim 6 further specifies only that the protein is (1) natively encoded by a nematode organism or (2) is encoded by a heterologous sequence introduced into the nematode or (3) shares at least 20% amino acid sequence identity in the metalloprotease and thrombospondin domains with (1) or (2), or is a chimeric protein. In the assay, the protein can retain the ability to direct migration of the gonadal cell or that activity can be conferred by the potential modulator. In any event, a suitable protein must be available to the nematode before any migration can take place. Thus, the assay can be used to assess defects in the protein provided.

The applicants' disclosure fully encompasses the scope of the protein as recited and claimed in Claims 6-10. For example, the first full paragraph on page 11 and the paragraphs that follow through page 17 fully support these claims. The disclosure on pages 17-19 describe using the applicants' system to assess potential for directing cell migration in the assay.

Although the applicants have not disclosed particular amino acid variants the metalloprotease and thrombospondin domains, the art is very familiar with the activity of those domains and, moreover, one can without undue experimentation use the disclosed system to assess whether a protein meeting the sequence identity criteria retains the migration function on whether another protein can rescue that function. The assay itself is very straightforward for a skilled artisan possessing the applicants' disclosure.

As an aside, the applicants note that since the filing of the application, a cDNA encoding human aggrecanase (a "human aggrecan-degrading metalloprotease" of Claim 9) was placed under the control of a promoter that drives expression in the migrating gonadal cell that controls organ shape. The construct was introduced into gon-1 mutant worms having no gon-1 activity and no gonadal cell migration. As predicted, the human aggrecanase partially rescued these gon-1 null mutants such that some animals exhibited some cell

migration. This is an example of a protein meeting the criteria of Claim 6 functioning in the assay of Claim 1 and a demonstration of the principal that proteins other than gon-1 can have a migration-directing activity in a nematode, even where that activity is not a natural activity of aggrecanase and had not previously been identified in the protein.

Claims 1-13 were also rejected under §112, first paragraph for an alleged lack of enablement. Applicants respectfully traverse the rejection. The Examiner asks whether gon-1 is the only gene that is responsible for gonadal cell migration in all the organisms or even in *C. elegans*. The Examiner's attention is directed to the first full paragraph on page 3 of the specification which indicates that gon-1 "is essential for extension of gonadal germline arms . . ." and that "in *C. elegans* hermaphrodites, gon-1 is required for migration of two distal tip cells to produce two elongated tubes, whereas in males, gon-1 activity is required for migration of a single linker cell to produce a single elongated tube. In gon-1 mutant hermaphrodites, the leader cells are born normally in the somatic gonadal cell lineage and function normally to promote germline proliferation, but they fail to migrate and do not support arm extension. Similarly in males, the leader cell does not move and no arm extension occurs." Thus, it is clear from the specification that gon-1 in *C. elegans*, and by analogy in other related nematodes, is decidedly an essential gene for gonadal cell migration whether or not it is the only gene responsible for gonadal cell migration. Thus, testing of a potential positive or negative modulator of gonadal cell migration can be accomplished in the identified nematode system.

Moreover, not only is the assay useful in nematodes that include gon-1, but also in systems in which a gon-1-substitute protein is used in the assay, along the lines of Claims 6-10. By imposing both structural and functional limitations on the nature of the permissible substitute protein, and in view of the understanding in the art of the important attributes of a metalloprotease domain and a thrombospondin domain, the claims are fully enabled over their entire scope.

Moreover, the amended claims now recite practicing the method in a nematode rather than a "target organism." Further, the nematode is selected from the group consisting of *C. elegans* and *C. briggsae*, a pair of closely related and very well characterized nematodes that can be used essentially interchangeably in assay systems. It would be unduly limiting to require the applicants to recite only *C. elegans* in the claims, as any skilled artisan would immediately adopt *C. briggsae* as the target organism in an effort to avoid the patent claims. *C. briggsae* is mentioned on page 12, line 5 as a suitable organism in which to practice the principles disclosed by the applicants. Applicants reserve the right to further expand the scope of the claimed target organism in due course.

The Examiner also suggests that the application does not provide any guidance as to how the claimed method would be carried out in *C. elegans*. Again applicants traverse the Examiner's suggestion. The prophetic example on page 27 fully describes administering a

potential modulating agent in an amount that is preferably several nanograms to several micrograms per milliliter. Those skilled in the art well understand that agents can be readily administered to *C. elegans* simply by including the agent in the culture medium or by injection and that no additional delivery steps are required. Moreover, the Examiner has already pointed to the specification at page 12 which discloses this and other methods for introducing an agent to the organism. Further, the specification refers the reader at page 12 to Volume 48 of Methods in Cell Biology, a standard comprehensive and well known reference to available methods and conditions for growing and monitoring *C. elegans* (and related nematodes).

Nothwithstanding these disclosures, the Examiner also asks how migration of a cell or sterility can indicate that the change is due only to a certain protein function and not to any other function. As was noted above, some amount of gon-1 activity is essential for any cell migration, whether that activity is supplied by a native, wild-type gon-1 or by a mutant gon-1 or by another protein within the scope of the claims or by a potential modulator that can confer upon the nematode an ability to migrate. As an aside, where the assay is intended to reveal modulators that provide or increase migration activity, the protein can lack that activity or can direct a low level of migration activity.

The true test of the assay compares cell migration activity in treated and untreated nematodes, as in any controlled assay. Thus, it is irrelevant whether the potential modulator has any effect upon the migration protein. What matters in the assay is whether the modulator can affect gonadal cell migration. The Examiner's comments about the effect upon the protein is an unfortunate red herring. The importance of providing an active protein in the nematode is to ensure that the cells are capable of migration. A goal of the assay is not to determine whether a potential modulator has an effect upon the protein but rather to determine whether the potential modulator has an effect upon cell migration. It is believed that the proposed claim amendments will clarify this to the Examiner's satisfaction.

The Examiner also asks whether any and all proteins that comprise a metalloprotease and thrombospondin motif have a role in gonad development or gonadal cell migration in the organisms. Again, the system provides a mechanism for assessing the activity of metalloprotease/thrombospondin motifs in a convenient system where the activity of a protein comprising those motifs in the system is now understood. Whether such a protein would naturally have that effect in its native host is, again, irrelevant. One nice advantage of the applicants' system is to be able to take those other proteins out of their original context and put them into a system in which their activity can be easily assayed or modulated. Applicants have noted above the successful substitution of human aggrecanase for gon-1 in the nematode system and have demonstrated that human aggrecanase can partially replace gon-1 activity, even though that is not known to be a function of aggrecanase and even though aggrecanase is not known to naturally have activity in gonadal cells. This is a proof of principle that

should extend to other proteins that contain metalloprotease/thrombospondin motifs. There is a separate and detailed understanding in the art of metalloprotease and thrombospondin domains and the nature of the sequences that are or are not characteristic of those motifs. The Examiner's attention is directed to the specification at page 12, line 28 through page 14, line 33 which relate to this point. Since the claimed assay can be used to find modulators that rescue migration activity in the assay, it is important not to unduly limit the nature of the gon-1-type protein provided in the nematode.

The Examiner also asked about the recitation of at least 20% amino acid sequence identity. Applicants trust that amended Claim 6 clarifies the applicants' intent with regard to that recitation. As noted above, a cell migration activity is not an essential attribute of the protein in the method. Rather, that activity can be provided by the potential modulator. The important point is that the assay system is a tester for metalloprotease/thrombospondin domain-containing proteins and, among other utilities, has utility in assessing the role of individual amino acids in those domains of proteins from various sources.

For all those reasons, reconsideration of the rejections under 35 U.S.C. §112, first paragraph is respectfully requested.

Rejections Under 35 U.S.C. §112, second paragraph

The Examiner imposed various rejections for indefiniteness, lack of antecedent basis, lack of clarity, vagueness, and for omission of an essential step. Each point raised by the Examiner is addressed in the set of amended claims. Reconsideration of the rejections under 35 U.S.C. §112 is respectfully requested.

Should the Examiner have any lingering concerns about the claims or the method itself, the Examiner is asked to contact the undersigned directly by telephone to expedite prosecution of this application.

Respectfully submitted,

Bennett J. Berson
Reg. No. 37,094
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL 608/251-5000
FAX 608/251-9166

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicants: Judith E. Kimble
Robert H. Blelloch

Date: April 13, 2001

Serial No.: 09/321,987

Group Art Unit: 1632

Filed: 05/28/99

Examiner: R. Shukla

For: AGENT AND METHOD FOR MODULATION OF CELL MIGRATION

File No.: 960296.95386

In the Specification:

On page 8, delete the paragraph beginning on line 8 and ending on line 19 and insert the following paragraph:

Fig. 1B shows a schematic map of *C. elegans* GON-1, the location of five protein-truncating stop mutants in GON-1 and a comparison to the protein structures of the murine ADAMTS-1 protein, and the bovine procollagen-I N-proteinase [(PN1P)] (P1NP) protein. From left to right, GON-1 includes a prodomain, a metalloprotease domain, a first cysteine rich region, a thrombospondin type I motif, a second cysteine rich region, and a plurality of thrombospondin type I-like motifs. The five mutants are identified as *q518 (aa591 TGG->TGA), e2551 (aa1069 TGG->TAG), e2547 (aa1229 TGG->TGA), q18 (aa1234 TGG->TAG)* W->stop, and e1254 (aa1345 CGA->TGA) R->stop).

In the Claims:

Please cancel Claims 11, 12, and 14-27 and amend Claims 1-8 and 13, as follows:

1. (Amended) A method for identifying in a nematode having a developing gonadal cell a modulator of [a protein that comprises] an activity of a protein for directing migration of the gonadal cell, wherein the protein comprises a metalloprotease domain and a thrombospondin domain, the nematode being selected from the group consisting of *C. elegans* and *C. briggsae*, the method comprising the steps of:

treating [a target organism having a developing gonadal cell responsive to the protein] the nematode with at least one potential modulator of gonadal cell migration; and

observing in the treated [target organism] nematode a change in migration or shape of the developing gonadal cell attributable to the presence of the at least one potential modulator, wherein a change in the migration or shape of the developing gonadal cell results in the identification of the modulator.

2. (Amended) A method as claimed in Claim 1 wherein migration of the developing gonadal cell in the [target organism] nematode before treatment is absent or reduced relative to a wild type individual.

3. (Amended) A method as claimed in Claim 1 wherein the treating step restores or enhances migration in the [target organism] nematode relative to migration before the treating step.

4. (Amended) A method as claimed in Claim 1 wherein migration of the developing gonadal cell in the [target organism] nematode before treatment is at a level of a wild type individual.

5. (Amended) A method as claimed in Claim 1 wherein the treating step reduces migration in the [target organism] nematode relative to migration before the treating step.

6. (Amended) A method as claimed in Claim 1 [wherein the target organism comprises a protein that comprises a metalloprotease domain and a thrombospondin domain], the protein being selected from the group consisting of a protein encoded by a native polynucleotide [coding] sequence, a protein encoded by a heterologous polynucleotide [coding] sequence introduced into the [target organism] nematode, a protein that shares at least 20% amino acid sequence identity in the metalloprotease and thrombospondin domains with either of the foregoing [and retains an ability to direct cell migration in the target organism], and a chimeric protein [encoded at least in part by at least one of the foregoing and] introduced into the [target organism] nematode, the polynucleotide [coding] sequence being under transcriptional control of a promoter active in a tissue located sufficiently close to the developing gonadal cell so as to signal the cell to migrate.

7. (Amended) A method as claimed in Claim 6, wherein the native polynucleotide [coding] sequence is *C. elegans gon-1*.

8. (Amended) A method as claimed in Claim 6, wherein the heterologous polynucleotide [coding] sequence is a homolog of *C. elegans gon-1*.

9. A method as claimed in Claim 8 wherein the homolog of *C. elegans gon-1* encodes a metalloprotease enzyme selected from the group consisting of murine ADAMTS-1 protein, bovine procollagen-1 N-proteinase, and human aggrecan-degrading metalloprotease.

10. A method as claimed in Claim 6 wherein the protein is truncated relative to a protein in a wild type individual.

11. (CANCEL) A method as claimed in Claim 1 wherein the target organism is a nematode.

12. (CANCEL) A method as claimed in Claim 11 wherein the target organism is a nematode selected from the group consisting of *C. elegans* and *C. briggsae*.

13. (Amended) A method as claimed in Claim 1 wherein the at least one potential modulator is selected from the group consisting of a nucleic acid molecule, a protein molecule, a sugar, a lipid, an organic molecule, a synthetic or natural pharmaceutical agent, and a mixture thereof.

In the Sequence Listing:

Please cancel the Sequence Listing in its entirety and replace it with the attached Sequence Listing.